Type of the Paper (Review)

Population Based Testing for Primary Prevention: a Systematic Review

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Abstract: The current clinical model for genetic-testing is based on clinical-criteria/family-history(FH) and a pre-defined mutation probability threshold. It requires people to develop cancer before identifying unaffected individuals in the family to target prevention. This process is inefficient, resource intense and misses >50% of individuals/mutation carriers at risk. Population genetic-testing can overcome these limitations. It is technically feasible to test populations on a large scale; genetic-testing costs are falling and the acceptability/awareness is rising. MEDLINE/EMBASE/Pubmed/CINAHL/PsychINFO databases were searched using a free-text and MeSH terms; reference lists of publications retrieved screened; additionally web-based platforms, Google, and clinical-trial registries were searched. Quality of studies were evaluated using appropriate check-lists. A number of studies have evaluated population-based BRCA-testing in the Jewish-population. This has been found to be acceptable, feasible, clinically-effective, safe, associated with high satisfaction rates and extremely cost-effective. Data support change in guidelines to population-based BRCA-testing in the Jewish-population. Population panel-testing for *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* gene mutations is the most cost-effective genetic-testing strategy in general-population women and can prevent thousands more breast/ovarian cancers than current clinical-criteria based approaches. A few ongoing studies are evaluating population-based genetic-testing for multiple cancer susceptibility genes in the general-population but more implementation studies are needed. A future population-testing programme could also target other chronic diseases.

Keywords: Population testing, genetic testing, BRCA, Jewish, general population, cancer prevention, primary prevention

1. Introduction

A number of moderate to high penetrance cancer-susceptibility genes (CSG) with well-established clinical utility have been identified over the last two decades, and testing for these is widely available in clinical practice. The prime, most well-known exemplars have been *BRCA1* and *BRCA2*. *BRCA1/BRCA2* carriers have a 17-44% risk of ovarian cancer (OC) and 69-72% risk of breast cancer (BC) till age 80 years.[1] The current model for genetic testing is still predominantly driven by family-history (FH) or clinical-criteria with testing undertaken in hospitals or specialist genetic clinics following informed pre-test counselling. These FH-based criteria have been used to calculate

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mutation probability with genetic testing offered over a pre-defined probability threshold. Clinical-criteria have been loosened and this threshold for offering testing has fallen over the years (from an earlier high of 20%), with most countries/health systems now offering *BRCA*-testing at about a 10% *BRCA*-mutation probability. A number of different models, ranging from standardized criteria to complex mathematical (Empirical/Mendelian) methodologies have been used to calculate mutation probability and are used in clinical practice. Carrier identification has numerous potential clinical benefits, which have been the main drivers for genetic testing. Effective options for prevention and/or screening are well-established for these mutation-carriers in clinical practice. Unaffected *BRCA*-mutation carriers can opt for: risk-reducing salpingo-oophorectomy (RRSO) to reduce their OC-risk;[2] as well as MRI/mammography screening, and chemoprevention with selective estrogen-receptor-modulators (SERM)[3] or risk-reducing mastectomy (RRM)[4] to reduce their BC-risk. Additionally, mutation identification enables informed reproductive and contraceptive choices which can impact risk, including timing of pill use, planning a family, as well as prenatal and pre-implantation genetic-diagnosis (PGD)[5]. Cancer affected carriers can opt for novel drugs like PARP inhibitors which improve survival as well as gain access to newer precision medicine based targeted therapeutics through clinical trials.[6-8]

Pre-test genetic-counselling is a fundamental element of international guidelines[9] for informed decision-making before genetic-testing. The model for counselling has evolved over the years, with the original Huntingdon Model involving a minimum of two 60 minute face-to-face pre-test counselling sessions[10] now archived as a fixture of the past. Telephone counselling, DVD-based and group based approaches have been found to be non-inferior to traditional 1:1 face-to-face counselling.[11-16] Over the years a wide variety of decision aids have been used as adjuncts to help informed decision making, such as booklets, pamphlets, audiotapes, computer-based programmes and web-based platforms. Another important recent development is the move away from traditional genetics clinics towards non-genetic clinicians undertaking routine pre-test counselling and testing at cancer diagnosis.[17]

1.1. The need for change

The current Clinical-criteria/FH-based system of genetic testing has many limitations. It is only moderately effective at identifying mutations and poor at ruling out the presence of one.[18] We[19] and others[20,21] have shown current testing-criteria miss >50% *BRCA*-carriers with a relevant cancer and an even higher proportion of unaffected carriers don't fulfil current genetic-testing criteria. There are a number of reasons for this including paternal inheritance, poor communication within and between families, inability to access health records, population migration, smaller nuclear families, lack of awareness and pure chance. Besides number of carriers are missed because they will have a probability below the clinical testing threshold (their *BRCA* probability is not nil or 0). Additionally the current approach requires individuals to be aware of their FH of cancer, understand its importance, and contact their GP or relevant health professional. The health professional in turn needs to understand the importance of this history and needs to refer to an appropriate genetics centre/ clinician. This gate keeper approach requires people to jump through a number of hoops. Lack of public and health professional awareness and complexity/inefficiency of the current structure and

testing pathway has led to restricted access and massive under-utilisation of genetic testing services.[22,23] Childers et al estimate that >70% BC and >80% OC patients eligible for genetic testing in the USA have never discussed this with a health professional.[22] We recently analysed recent NHS genetic-laboratory *BRCA*-testing data from 1993-2014 across a 16 million Greater-London population and found that <3% of estimated *BRCA*-carriers had been identified to date.[23] Our forecasting models suggest detection-rates using the current system are inadequate to identify all *BRCA*-carriers in the population and even doubling them will need 165-years to identify the 'clinically detectable' proportion of *BRCA*-carriers (~50% don't fulfil clinical-testing criteria, remaining undetectable).[23] Given the small proportion of unaffected individuals getting cancer annually, even addition of unselected case series testing while useful in identifying the pool of individuals without strong FH of cancer, will require ~250 years to identify residual undetected *BRCA* carriers.[23] Why do we need to wait for decades for people to develop cancer before identifying mutation carriers and their at risk family members? With the effective options for cancer-risk management and prevention available for high-risk women, this raises serious questions about the adequacy of the current clinical-criteria/FH-based approach. A number of these limitations can be overcome by offering unrestricted/unselected population based testing.

Next generation sequencing driven high throughput testing coupled with advances in bioinformatics has technologically enabled large scale population wide testing. Falling costs of testing and increasing population awareness of cancer genetics and its implications offers a timely opportunity to apply this knowledge and technology on a broad population-scale to provide an important impetus in healthcare towards disease prevention. We present a systematic review of the literature on population-based germline testing for *BRCA* gene mutations. We also explore future applicability and potential for this strategy across other CSGs/chronic disease.

2. Methods

2.1. Search strategy and selection criteria

We systematically reviewed the current literature on population-based germline testing for BRCA-mutations using a comprehensive three step search strategy to identify relevant studies. First we searched the following five databases from inception to August 30 2018: MEDLINE, EMBASE, Pubmed, CINAHL, and PsychINFO. A common search strategy (Table-1) was developed for database searching using a combination of free text and controlled vocabulary (MeSH terms). Second, reference lists of publications retrieved in the first step were screened for relevant studies. Third, we searched additional web-based platforms including specialised journals, Google searches for grey literature, conference proceedings and clinical trial registries (ISRCTN registry/ClinicalTrials.gov registry).

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Objective	To identify published literature on unselected population based germline testing
Data sources	A systematic review of articles with the use of MEDLINE (1946 to August 2018), EMBASE (1974 to August 2018), Pubmed (1996 to August 2018), CINAHL (1937 to August 2018), PsychINFO (1806 to August 2018)
Search strategy	49 searches were undertaken using the below PICO framework: **P**articipants: unaffected men/women **I**ntervention: unselected population genetic testing **C**omparison: family history/clinical criteria genetic testing **O**utcomes: acceptability; detection rate; satisfaction; quality of life; cost-effectiveness of unselected genetic testing
1. (LOW RISK).ti,ab	
2. exp "LOW RISK"/	
3. (POPULATION RISK).ti,ab	
4. exp "POPULATION RISK"/	
5. 1 OR 2 OR 3 OR 4	
6. (CANCER).ti,ab	
7. exp "CANCER"/	
8. 6 OR 7	
9. (POPULATION GENETIC TESTING).ti,ab	
10. exp "POPULATION GENETIC TESTING"/	
11. (UNSELECTED GENETIC TESTING).ti,ab	
12. exp "UNSELECTED GENETIC TESTING"/	
13. 9 OR 10 OR 11 OR 12	
14. 8 AND 13	
15. (FAMILY HISTORY).ti,ab	

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16. exp "FAMILY HISTORY "/
17. 15 OR 16
18. (GENETIC TESTING).ti,ab
19. exp "GENETIC TESTING"/
20. 18 OR 19
21. 8 AND 17 AND 20
22. (BRCA).ti,ab
23. exp "BRCA"/
24. (BRCA AND "1 OR 2").ti,ab
25. exp "BRCA AND 1 OR 2"/
26. (BRCA AND 1).ti,ab
27. exp " BRCA AND 1"/
28. (BRCA AND 2).ti,ab
29. exp "BRCA AND 2"/
30. 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29
31. 8 AND 30
32. 14 OR 21 OR 31
33. (ACCEPTABILITY).ti,ab
34. exp "ACCEPTABILITY"/
35. 33 OR 34
36. (DETECTION RATE).ti,ab
37. exp "DETECTION RATE"/
38. 36 OR 37
39. (SATISFACTION).ti,ab
40. exp "SATISFACTION"/
41. 39 OR 40

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42. (QUALITY OF LIFE).ti,ab	
43. exp "QUALITY OF LIFE"/	
44. 42 OR 43	
45. (COST EFFECTIVE).ti,ab	
46. exp "COST EFFECTIVE"/	
47. 45 OR 46	
48. 35 OR 38 OR 41 OR 44 OR 47	
49. 5 AND 32 AND 48	
Eligibility criteria	Unselected, unaffected individuals at population level risk undergoing genetic testing for cancer predisposing genes; full text articles in English language.
Data extraction	Citations, abstracts extracted and reviewed by FG. Relevant papers reviewed by authors FG and RM.
Conclusion	Population genetic testing can overcome the limitations of family history/clinical criteria genetic testing. The technology to test populations on a large scale is available and the cost of testing is falling. Population based *BRCA* testing has been evaluated in the Jewish population and found to be acceptable, clinically effective, safe and cost-saving. However, these data cannot be 'directly' extrapolated to the non-Jewish general population. While recent data suggest genetic testing for breast/ovarian cancer gene mutations could be cost-effective in general population women too, additional research including implementation studies in the general population are needed to address various knowledge gaps before that step can be considered.

Table-1. Search strategy for literature search

Predefined inclusion criteria were unselected, unaffected individuals at population level risk undergoing genetic-testing for cancer predisposing genes. Outcomes investigated in relation to population genetic testing were: 1) acceptability, 2) testing uptake, 3) mutation detection rate, 4) satisfaction, 5) quality-of-life, 6) psychological health, 7) genetic counselling, 8) knowledge, 9) risk perception, 10) cost-effectiveness.

2.2. Data extraction and quality assessment

Data were extracted using a standardised, predesigned data extraction sheet in Microsoft Excel 2013. Four main categories of data were extracted: methodological characteristics of each study, study population, details of interventions and reported outcome measures pertaining to population genetic

testing. The quality of the studies was assessed depending on study design, using the following checklists: Quality of Health Economic Studies (QHES) checklist,[24] Critical Appraisal Skills Programme (CASP) qualitative research checklist, [25]Jadad scale for reporting randomized controlled trials[26] and Methodological Index for Non-Randomized Studies (MINORS) checklist.[27]

2.3. Data analysis

We tabulated characteristics and reported outcome measures of all studies for qualitative synthesis.

3. Results

Figure-1 provides the flow chart outlining the search outcomes and study selection process. Searches of electronic databases and reference lists generated 323 references. On evaluation of all titles and abstracts, 32/323 articles were potentially eligible for detailed assessment. 26/32 met our inclusion criteria for qualitative synthesis.[19-21,28-50] Relevant studies on population testing and design/outcomes/quality are summarised in Table-2. Table-3 encapsulates the main findings/conclusion from each study.

3.1. The Jewish *BRCA* Model

The majority of the evidence base for population-based testing currently comes from *BRCA* founder mutation testing (as the genetic disease model) in the Jewish population (population model). Six studies describe attitudes, interest, intention, barriers, and facilitators of BRCA testing in the AJ population (Table-2, Table-3).[29,30,45-47,51] Four main studies have evaluated the impact of unselected population-based *BRCA*-testing in the Jewish population: Two Israeli cohort studies (8195 men & 1771 women/men)[20,52]; One Canadian cohort study (2080 women)[21]; and one UK randomised controlled trial (RCT) (1034 women and men)[19]. Details of these studies and published outputs are described in Table-2 and Table-3. These studies demonstrate that population-based *BRCA*-testing in the Jewish population is feasible, acceptable, safe, can be undertaken in a community setting, and identifies >50% additional *BRCA*-carriers who would have been missed by traditional clinical-criteria. RCT data show no significant difference in psychological well-being and quality-of-life outcomes between population-based and FH/Clinical-criteria based *BRCA*-testing approaches.[19] Overall anxiety and uncertainty with *BRCA*-testing were found to decrease with time.[19] Israeli and Canadian cohort data show increased anxiety and distress in identified mutation carriers at 6 months/1 year.[52,53] However, overall satisfaction rates are high for all participants (>91%) and similar to non-carriers.[52] Hence, outcomes seen with population-based testing appear to be similar to those reported from high-risk clinics.[54]

Both Israeli and UK data suggest testing uptake and satisfaction rates are higher for testing undertaken through self-referral in ambulatory or community centres compared to hospital ascertainment.[19,52] Qualitative data re-confirm overall satisfaction with population-based *BRCA*-testing reported with quantitative analyses, with 81% carriers and 90% non-carriers interviewed expressing unequivocal positive attitudes towards the *BRCA*-testing experience.[51] Barriers and

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facilitators reported with population-testing are similar to those found in high risk clinics. Other emergent themes reported include the need for incorporating testing into routine practice through primary care and via non-genetic clinicians as well as preservation of autonomy in decision making.[51] Familial communication following testing has been found to be associated with overall satisfaction with the process and FH of cancer. Initial cascade testing rates are higher in first-degree than second-degree relatives.[33]

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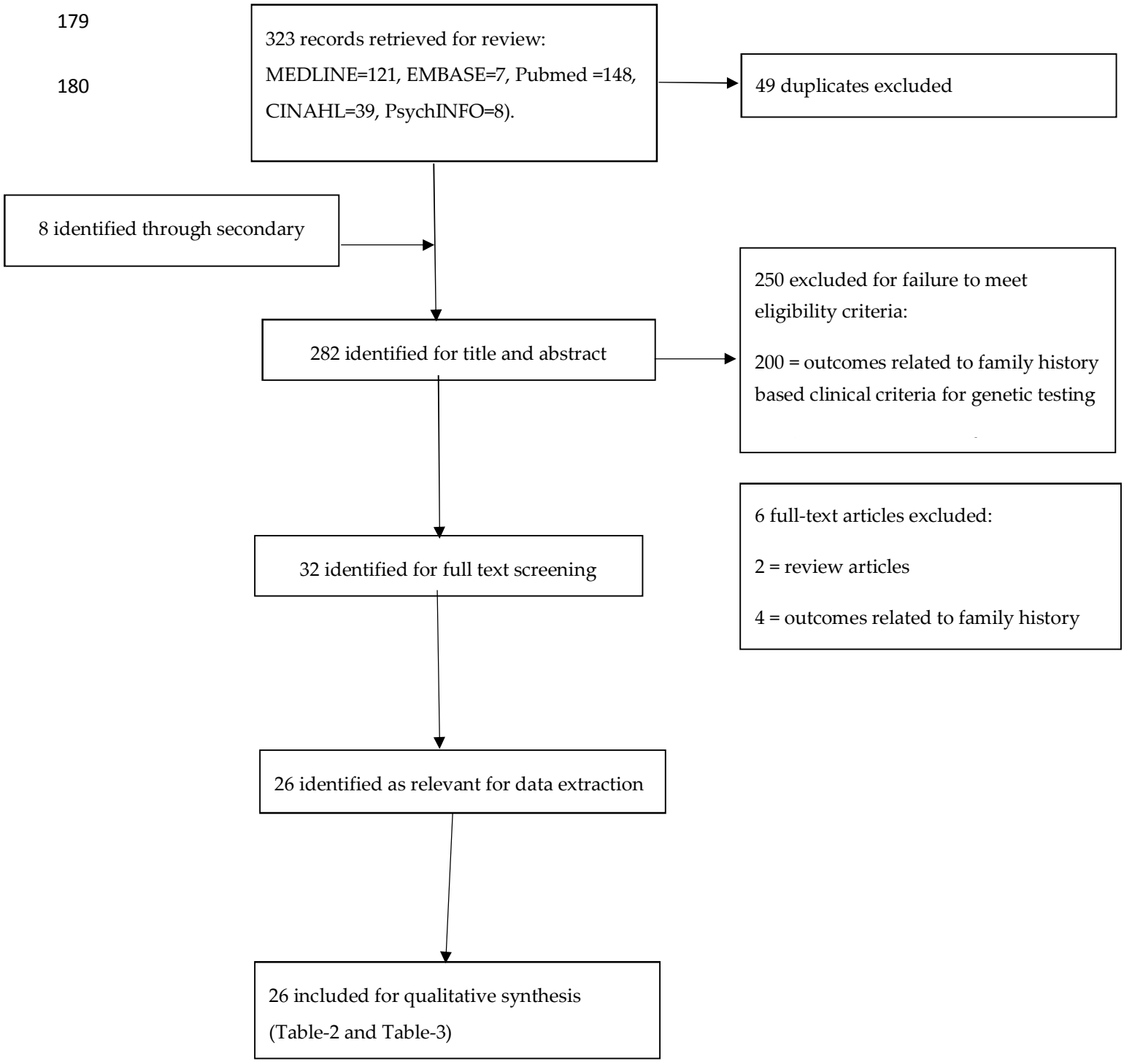

Figure-1. Flowchart of study selection

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Publication/registered study	Country	Sample size (n)	Study design	Population	Intervention	Outcomes	Follow up	Quality of study methodology
Brown, 1995[28]	US	N/A	Cost-effectiveness analysis	General population	PGT for *MSH2*/*MLH1*	Cost per life year gained	N/A	31/100[£]
Cousens, 2017[29]	Australia	370	Prospective, survey	AJ women	Survey on *BRCA1*/*BRCA2* PGT	Attitudes; acceptability; interest	None	13/16[#]
Gabai-Kapara, 2014[20]	Israel	8195 (& 694 relatives of carriers)	Prospective cohort	AJ men/women	PGT for AJ *BRCA1*/*BRCA2* founder mutations	Risk of BC/OC in female carriers ascertained through an unaffected male index subject	Not reported	12/16[#]
Lehmann, 2002[30]	US	200	Prospective, survey	AJ women	Telephone survey on *BRCA1*/*BRCA2* PGT	Attitudes; acceptability	None	12/16[#]
Lieberman, 2017[31]	Israel	36	Qualitative	AJ men/women	Semi structured interviews in individuals undergoing PGT for AJ *BRCA1*/*BRCA2* founder mutations	Motivators/barriers to testing; satisfaction	18 months	Good~
Lieberman, 2017[32]	Israel	1,771	Prospective cohort	AJ men/women	PGT for AJ *BRCA1*/*BRCA2* founder mutations	Uptake; post-test counselling compliance; satisfaction; anxiety; distress; increase in knowledge	6 months	12/16[#]
Lieberman, 2018[33]	Israel	1,771	Prospective, cohort	AJ men/women	PGT for AJ *BRCA1*/*BRCA2* founder mutations	Familial communication; cascade testing	2 years	12/16[#]

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Manchanda, 2015[19] (ISRCTN73338115)	UK	1,034	Randomised controlled trial	AJ men/women	PGT versus FH based testing of AJ *BRCA1/BRCA2* founder mutations	Acceptability; psychological impact; QoL	3 months	5/5*
Manchanda, 2015[34] (ISRCTN73338115)	UK	N/A	Cost-utility analysis	AJ women	PGT versus FH based testing for AJ *BRCA1/BRCA2* founder mutations	Incremental cost effectiveness ratio per quality adjusted life year	N/A	96/100£
Manchanda, 2016[35] (ISRCTN73338115)	UK	936	Cluster randomised non-inferiority trial	AJ men/women	DVD assisted versus face-to-face pre-test counselling in individuals undergoing PGT of AJ *BRCA1/BRCA2* founder mutations	Uptake; cancer risk perception; increase in knowledge; counselling time; satisfaction	N/A	4/5*
Manchanda, 2017[36]	UK, US	N/A	Cost-utility analysis	AJ women	PGT versus FH based testing for AJ *BRCA1/BRCA2* founder mutations with differing AJ ancestry	Incremental cost effectiveness ratio per quality adjusted life year	N/A	90/100£
Manchanda, 2018[37]	UK, US	N/A	Cost-utility analysis	General population women	PGT versus FH based testing of *BRCA1/BRCA2/ RAD51C/RAD51D/BRIP1/PALB2* mutations	Incremental cost effectiveness ratio per quality adjusted life year	N/A	96/100£
Meisel, 2016[38]	UK	829	Prospective, cohort	General population women	Survey	Interest; attitudes	None	12/16#

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Meisel, 2017[39]	UK	1031	Randomised experimental survey	General population women	Brief information versus lengthier information to inform decision making about participating in a study (PROMISE study) on PGT for OC	Knowledge; intention; attitudes towards taking part in the PROMISE study	None	3/5*
Meisel, 2017[40]	UK	837	Cross-sectional survey	General population women	Survey on *BRCA1/BRCA2* PGT	Anticipated health behaviour change; perceived control to disclosure of OC/BC risk	None	11/16#
Metcalfe, 2010[21]	Canada	2080	Prospective, cohort	AJ/SJ women	PGT for Jewish *BRCA1/BRCA2* founder mutations	Mutation prevalence	None	14/16#
Metcalfe, 2010[41]	Canada	2080	Prospective, cohort	AJ/SJ women	PGT for Jewish *BRCA1/BRCA2* founder mutations	Satisfaction; cancer related distress; cancer risk perception	1 year	14/16#
Metcalfe, 2012[42]	Canada	2080	Prospective, cohort	AJ/SJ women	PGT for Jewish *BRCA1/BRCA2* founder mutations	Cancer related distress; uptake of cancer risk reduction options	2 years	14/16#
Patel, 2018[43]	UK, US	N/A	Cost-utility analysis	SJ women	PGT versus FH based testing for SJ BRCA1 founder mutations	Incremental cost effectiveness ratio per quality adjusted life year	N/A	90/100£
Rubinstein, 2009[44]	US	N/A	Cost-utility analysis	AJ women	PGT for AJ *BRCA1/BRCA2* founder mutations versus 'no' genetic testing	Incremental cost effectiveness	N/A	71/100£

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						ratio per quality adjusted life year		
Schwartz, 2001[45]	US	391	Randomised controlled trial	AJ women	PGT for *BRCA1/BRCA2* educational material versus general BC education control material	Knowledge; perception of risks and limitations; interest	1 month	3/5*
Shkedi-Rafid, 2012[46]	Israel	14	Qualitative	Unaffected BRCA1/BRCA2 AJ female carriers ascertained following a positive test result in a male family member who underwent PGT	Semi structured in-depth interviews on PGT for AJ *BRCA1/BRCA2* founder mutations	Emotional implications; motivations; consequences; attitudes	None	Good~
Tang, 2017[47]	US	243	Cross-sectional survey	Orthodox AJ women	Survey on PGT for *BRCA1/BRCA2*	Knowledge; perceived BC risk/worry; religious/cultural factors affecting decision making	None	13/16#
Warner, 2005[48]	Australia	300	Prospective, cohort	AJ men/women	PGT for APC I1307K mutation, but non-disclosure of results	Acceptability; facilitators and barriers to testing	None	10/16#
PROMISE Feasibility Study[49] (ISRCTN54246466)	UK	100	Prospective, cohort	General population women	PGT for *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* and subsequent risk stratified screening and prevention	Acceptability; risk perception; cancer worry; QoL; stratification of OC risk; uptake of risk management options; satisfaction/regret; follow up completion rate; telephone helpline use; decision aid use	6 months	N/A

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The Screen Project[50]	Canada	10,000	Prospective, cohort	General population men/women	PGT for *BRCA1/BRCA2*	Satisfaction; cancer worry	Not reported	N/A

Table-2. Publications and registered studies reporting population genetic testing outcomes

PGT – population genetic testing; FH – family history; AJ – Ashkenazi Jewish; SJ – Sephardi Jewish; QoL – quality of life; BC – breast cancer; OC – ovarian cancer; PROMISE - Predicting risk of ovarian malignancy improved screening and early detection feasibility study; ICER – incremental cost-effective ratio; QALY – quality adjusted life year

£Quality of study assessed using Quality of Health Economic Studies (QHES) checklist

˜Quality of study assessed using the Critical Appraisal Skills Programme (CASP) qualitative research checklist

*Quality of study assessed using the Jadad scale for reporting randomized controlled trials

#Quality of study assessed using the Methodological Index for Non-Randomized Studies (MINORS) checklist

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Publication/registered study	Findings
Brown, 1995[28]	Exploratory analysis for cost effectiveness of PGT for MMR gene mutations *MLH1*/*MSH2* compared to FH testing. PGT may be cost-effective if the base case analysis assumes a restrictive set of assumptions most favourable to the outcome with respect to prevalence, costs, clinical efficacy of screening and preventive interventions.
Cousens, 2017[29]	96.8% support a Jewish *BRCA1*/*BRCA2* testing program; 65.6 % interested in undergoing PGT. Interest in population based BRCA testing was higher in women <50 years than women >50 years.
Gabai-Kapara, 2014[20]	For female relatives with *BRCA1*/*BRCA2* mutations identified through unaffected AJ male relatives, cumulative risk of developing BC/OC by age 60 and 80 respectively were 0.60/0.83 for BRCA1; 0.33/0.76 for BRCA2 carriers. 2.17% AJ carry a *BRCA1*/*BRCA2* mutation.
Lehmann, 2002[30]	40% AJ women interested in PGT for *BRCA1*/*BRCA2*, 40% not interested, and 20% uncertain. Increased interest associated with desire to obtain information on children's risk and valuing information for its own sake. 17% expressed concern or discomfort about Jews being offered BRCA1/2 testing. Increased concern about genetic discrimination associated with highly educated women.
Lieberman, 2017[31]	Motivators for *BRCA* testing: knowledge of *BRCA* status to enable cancer risk reduction; health-empowerment. Barriers: lack of physician awareness/support. Routinization of testing can overcome medical and social barriers. Importance of maintaining/safeguarding autonomy of choice and providing adequate post-test services was highlighted.
Lieberman, 2017[32]	*BRCA* testing uptake 67%. Post-test counselling compliance 100% for carriers; 89% for non-carriers with FH. All groups had high satisfaction (>90%). At 6 months, carriers had significantly increased distress/anxiety; greater knowledge; similar satisfaction to non-carriers. 90% recommended PGT for *BRCA* in the AJ community. Proactive recruitment through a clinical service captured older women more unselected for FH compared to self-referral based recruitment.
Lieberman, 2018[33]	97% carriers informed at least one relative. FH and higher Satisfaction With Health Decision scores predicted results communication. FDRs had a higher rate of cascade/predictive testing than SDRs. Female relatives had a higher level of cascade testing than male relatives.
Manchanda, 2015[19] (ISRCTN73338115)	Compared with FH based testing, PGT for *BRCA1*/*BRCA2* AJ founder mutations, does not adversely affect short-term psychological/QoL outcomes and may detect 56% additional BRCA carriers. 56% of carriers do not fulfil clinical criteria for genetic testing, and the BRCA1/2 prevalence is 2.45%.

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Manchanda, 2015[34] (ISRCTN73338115)	PGT for AJ *BRCA1*/*BRCA2* founder mutations is cost saving with a baseline discounted ICER of -£2079/QALY. PGT lowered OC/BC incidence by 0.34% and 0.62% respectively. Assuming 71% testing uptake, this leads to 276 fewer OC and 508 fewer BC cases. Overall, reduction in treatment costs leads to a discounted cost savings of £3.7 million in the UK population.
Manchanda, 2016[35] (ISRCTN73338115)	DVD assisted counselling for PGT is non-inferior to face-to-face counselling for increase in knowledge; counselling satisfaction; risk perception and is equivalent for uptake. 98% found DVD length/information satisfactory. 85–89% felt it improved understanding of risks/benefits/implications/purpose of PGT. 95% would recommend it to others.
Manchanda, 2017[36]	PGT for *BRCA* mutations is cost-saving in AJ with 2-4 grandparents (22-33 days life gained) in the UK and 1-4 grandparents (12-26 days life-gained) in the US. It is extremely cost-effective in women in the UK with 1 AJ grandparent with ICER=£863/QALY; 15 days life gained. PGT remains cost-effective in the absence of reduction in BC risk from RRSO; at lower RRM (13%) or RRSO (20%) rates.
Manchanda, 2018[37]	Population panel genetic testing for *BRCA1*/*BRCA2*/*RAD51C*/*RAD51D*/*BRIP1*/*PALB2* mutations is the most cost-effective genetic testing strategy compared with current policy: ICER=£21,599.96/QALY or $54,769.78/QALY (9.34 or 7.57 days' life-expectancy gained). PGT for *BRCA1*/*BRCA2*/*RAD51C*/*RAD51D*/*BRIP1*/*PALB2* testing can prevent 1.86%/1.91% of BC and 3.2%/4.88% of OC in UK/US women: 657/655 OC cases and 2420/2386 BC cases prevented per million.
Meisel, 2016[38]	85% reported they would 'probably' or 'definitely' take up PGT for OC which increased to 88% if test also informed BC risk. 92% anticipated they would 'probably' or 'definitely' participate in risk-stratified OC screening. University level education is associated with lower anticipated uptake of PGT.
Meisel, 2017[39]	No significant differences between participants receiving brief versus lengthier information to inform decision making in terms of OC knowledge/intention to participate in OC screening following PGT. 74% reported they would participate in OC screening based on PGT assessment.
Meisel, 2017[40]	UK women anticipate that they would engage in positive health behaviour changes in response to BCOC risk disclosure.72% reported 'I would try harder to have a healthy lifestyle'; 55% felt 'it would give me more control over my life'. Associations were independent of demographic factors or perceived risk of OC/BC.
Metcalfe, 2010[21]	Overall BRCA1/BRCA2 prevalence in unselected Jewish women undergoing PGT was 1.1% (0.5% for *BRCA1* and 0.6% for *BRCA2*). Only 45% met clinical testing criteria.
Metcalfe, 2010[41]	In Jewish *BRCA* carriers, mean BC risk perception increased significantly from 41.1% to 59.6% after receiving a positive result. Among non-carriers, BC risk perception decreased non-significantly, from 35.8% to 33.5%. Cancer related distress increased significantly for carriers, but not in non-carriers. 92.8% satisfied with PGT.

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Metcalfe, 2012[42]	Within 2 years of receiving a positive Jewish *BRCA* founder mutation result, 11.1% had RRM; 89.5% RRSO. Mean BC risk estimated to be 37.2% at time of testing versus 20.9% at 2 years post-testing. Distress decreased between 1 and 2 years for women with RRM/RRSO and for women with only RRSO but not for those with no surgery.
Patel, 2018[43]	PGT is cost-effective for SJ *BRCA1* founder mutation. It results in 12 months (QALY=1.00) gain in life expectancy. Baseline discounted ICER for UK PGT = £67.04/QALY; US population= $308.42/QALY. PGT remains cost effective in UK/US, even if premenopausal RRSO doesn't reduce BC risk or if HRT compliance is nil.
Rubinstein, 2009[44]	Compared to a no testing policy, PGT for AJ *BRCA1*/*BRCA2* founder mutations is cost-effective and would result in 2,811 fewer cases of OC, with a life expectancy gain of 1.83 QALYs among carriers. At a cost of $460 for founder mutation testing, the cost of the program is $8,300/QALY.
Schwartz, 2001[45]	Compared to the BC education control material, the PGT education material led to increased knowledge; increased perception of the risks/limitations of testing; and a decreased interest in obtaining a *BRCA1*/*BRCA2* test.
Shkedi-Rafid, 2012[46]	Having no FH of cancer was a source of optimism but also confusion; engaging in intensified medical surveillance and undergoing preventive procedures was perceived as health promoting but also induced a sense of physical/psychological vulnerability; overall support for population *BRCA* testing in the AJ community, with some reservations.
Tang, 2017[47]	49% had adequate genetic testing knowledge; 46% had accurate BC risk perceptions. 20% reported they probably/definitely will get tested; 28% probably/definitely will not get tested; 46% had not thought about *BRCA* testing. Adequate genetic testing knowledge, higher BC risk, and overestimation of risk is associated with PGT intention. Cancer prevention and effect on children were the most important factors affecting testing intention.
Warner, 2005[48]	Following pre-test counselling 94% acceptability for PGT for colorectal cancer, but participants were not disclosed results. Facilitators: desire for information for their families; to decrease personal cancer risk. Barriers: insurance discrimination; test accuracy; confidentiality.
PROMISE Feasibility Study[49] (ISRCTN54246466)	Not reported. Study closed to recruitment and in follow up phase.
The Screen Project[50]	Not reported. Study actively recruiting.

190 **Table-3.** Findings of publications and registered studies reporting population genetic testing outcomes

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191 PGT – population genetic testing; FH – family history; AJ – Ashkenazi Jewish; QoL – quality of life; BC – breast cancer; OC – ovarian cancer; FDR – first degree
192 relative; SDR – second degree relative; ICER – incremental cost-effective ratio; QALY – quality adjusted life year

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For large-scale, population-based genetic-testing to become feasible/practical it is necessary to move away from the cost and time intensive 'traditional face-to-face' genetic-counselling[55] approach. A UK non-inferiority cluster-randomised trial, in the Jewish population showed that DVD-based pre-test counselling for population *BRCA*-testing is an effective, acceptable, non-inferior, time-saving and cost-efficient alternative to traditional genetic-counselling.[15] Other studies in high-risk women have established telephone-counselling is an effective non-inferior alternative to traditional genetic-counselling.[13] The Israeli and Canadian population-based studies successfully undertook *BRCA*-testing without pre-test counselling, and provided post-test counselling. Around 50% of *BRCA*-carriers and 20% of overall participants in the Canadian population-based study expressed a preference for pre-test counselling after receiving their results.[53] Nevertheless, high satisfaction rates (91-95%) are reported in all (UK/Israeli/Canadian) population-based *BRCA*-testing studies. A recent UK pilot study has shown acceptability of a web decision-aid plus helpline and post-test counselling approach for population-based testing.[56] Robust RCT data comparing pre-test counselling with decision-aid and helpline or post-test only counselling alone are lacking.

An initial paper confirms the cost-utility of population testing compared to no testing.[44] Three published analyses have evaluated cost-effectiveness of population-based *BRCA*-testing compared to current standard of clinical-criteria/FH testing in: the AJ population,[57] the AJ-population with varying AJ-ancestry[58] and the Sephardi-Jewish population.[59] These show that *BRCA*-testing in the Jewish-population is extremely cost-effective compared to FH-based testing. In fact in most published scenarios the intervention is cost-saving for both UK and USA health systems,[58] saving both lives and monies. Overall data thus strongly support the introduction of population-based *BRCA*-testing in the Jewish population. It is time guidelines change to reflect this.

The challenge of implementation: There is no single best/ideal model for implementing population-based *BRCA*-testing in the Jewish community. It is likely that different/bespoke models will be needed for various health systems and contexts. Implementation will need development of testing pathways through a community or primary care based approach outside the traditional hospital based genetics clinic model, particularly in regions with large or dense Jewish populations. Areas with small or sparse populations could even be absorbed within the current clinical genetics system through changes in testing criteria. Implementation will require significant efforts towards engagement of community leaders, charities, stakeholders, opinion makers and Rabbis across all sections of the community. Additionally downstream pathways for management of unaffected carriers (including genetics services, gynaecologists, breast clinicians and screening and prevention services) will need expanding or establishing. This will need integration into GP networks to ensure adequate infrastructure and coherent pathways for managing newly identified mutation carriers. This needs to be coupled with information campaigns to increase both public and health professional awareness.

3.2. Other founder populations

Specific *BRCA* founder mutations have been described in a number of other founder populations (in addition to the Jewish population). These include Polish, French, Swedish, Norwegian, Dutch, Hispanic, Malaysian, Afro-American, Pakistani, Filipino, Inuit and Bahamian populations.[60-62]

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Findings of *BRCA* founder mutation testing studies from the Jewish population could also have implications for *BRCA*-testing in other founder populations. However, it is difficult to currently generalise these beyond this to the rest of the non-founder general population. The Polish 'Twoj Styl' study offered Polish *BRCA1* founder mutation testing to 5024 women through a magazine advertisement.[63] Post-test counselling was provided to mutation carriers identified and high satisfaction rates (97%) reported overall. However, this was not true unselected population testing as there was ascertainment bias with testing offered only to women with cancer or a FH of breast/ovarian cancer.

3.2. General Population and Panel Testing

Next generation sequencing has enabled testing of multiple CSGs at the same time, i.e. Panel testing. This is now being implemented in clinical genetics for women at increased risk fulfilling usual clinical-criteria. Population-based testing too can incorporate multiple genes on a NGS panel. The panel of genes needs to have established analytic validity (sensitivity, specificity, reliability, and assay robustness- to reliably and accurately measure the genotype) and clinical validity (test's ability to reliably and accurately predict the associated disorder/ phenotype).[64] A key unassailable principle underpinning extending panel testing to a population-based setting is only testing for those genes which have well-established 'clinical utility' i.e. demonstrable clear net clinical benefit (clinically effective) which can impact disease outcome.[64] A number of genes widely available or offered through panels by gene testing companies/laboratories do not yet have well-established clinical utility. However, the list of genes with proven clinical utility will evolve and expand in the coming years.

A number of other moderate/high penetrance CSGs (in addition to *BRCA1*/*BRCA2*) can be incorporated into a population testing panel. Amongst the BC genes, *PALB2* confers non-syndromic quasi-Mendelian susceptibility to BC (BC-risk till age 80 years =44%)[65] for which equivalent interventions of MRI screening / preventive mastectomy are now offered to mutations carriers, and hence, *PALB2* can be incorporated. Although *ATM* and *CHEK2* are offered on some commercial panels, clinical testing of these genes is not currently routinely undertaken in most centres as the risks conferred by mutations in these genes are moderate (RR~1.5-2) and MRI/mastectomy not routinely offered for this. Hence, these are probably currently best left out of a population testing panel. Amongst the newer moderate risk OC genes, risk estimates for *RAD51C*, *RAD51D* and *BRIP1* (OC-risks ~6-11%) have been recently validated. We showed that surgical prevention (RRSO) is cost-effective at ≥4-5% OC-risk.[66,67] This enables clinical-utility for clinical-testing for these newer moderate OC-risk genes and the option of surgical prevention in unaffected women. Testing for these genes is now incorporated into clinical practice[68] and can be included in a population-based panel. Additionally Lynch-Syndrome (LS) *MLH1*/*MSH2*/*MSH6* mismatch-repair (MMR) genes have a 40-60% risk of colorectal-cancer, 30-45% risk of EC and 6-14% risk of OC.[69] LS/MMR-carriers can benefit from 1-2 yearly colonoscopies for colorectal-cancer screening and opt for daily aspirin[70] or prophylactic hysterectomy-&-oophorectomy for cancer prevention.[71] Amsterdam-II or Bethesda criteria used to identify *MLH1*/*MHS2*/*MSH6* carriers in clinical practice miss 55-70% or 12-30% (respectively) of these *MLH1*/*MHS2*/*MSH6* carriers[72] even amongst those with cancer. Thus, *MLH1*/*MHS2*/*MSH6* are also potential candidate CSGs that can be included in an extended

population germline testing panel. Overall these mutations account for around 15%-20% OC,[73] 6% BC,[74] 4-6% EC[75] and 4% bowel-cancers.[76]

Initial survey based data suggest that population-testing for OC gene mutations for risk stratification may be acceptable to 75% women[39] and 72% women anticipate they would engage in positive health behaviour changes in response to BC/ OC risk disclosure following genetic testing.[40] An ongoing UK pilot study (ISRCTN54246466) shows feasibility of counselling and recruitment for panel genetic-testing for multiple moderate-high penetrance OC genes in unselected general-population women ascertained through primary care.[56] The team in Toronto have implemented unselected *BRCA* testing for general population Canadian women and men over 18 years who are willing to pay for this themselves, through a Direct to Consumer testing model within 'The Screen Project' (http://www.thescreenproject.ca/) study. We recently evaluated the cost-effectiveness of population-based panel testing for OC and BC gene mutations (*BRCA1*/*BRCA2*/*RAD51C*/*RAD51D*/*BRIP1*/*PALB2*) by comparing this strategy to the usual clinical-criteria/FH based testing for both UK and US health systems.[37] Modelling showed that population-based panel testing for BC/OC CSGs was more cost-effective than any currently used clinical-criteria/FH-based strategy: either clinical-criteria/FH-based BRCA-testing or clinical-criteria/FH-based panel testing. The ICER (incremental cost-effectiveness ratio) were well below the UK £30,000/QALY (ICER= £21,599.96/QALY) and USA $100,000/QALY (ICER=$54,769.78/QALY) thresholds in the UK and USA respectively. Sensitivity analyses demonstrated that population-testing was the cost-effective and the preferred strategy in 84% UK and 93% USA simulations respectively. This could potentially prevent thousands more BC and OC cases over and above current policy. This was estimated to be 17505 OC and 64493 BC cases prevented in UK women, and 65221 OC and 237610 BC cases prevented in US women.

However, cost-effectiveness modelling, like all such analyses incurs assumptions, and further research is necessary for prospective validation of some key assumptions. Jewish data cannot be directly extrapolated or generalised to the non-Jewish general-population and general population implementation studies are necessary to evaluate the impact and reconfirm cost-effectiveness of population-based panel testing. More data are needed on uptake rates of screening and prevention options in mutation carriers without a strong FH of cancer. A critical issue which needs addressing is the management of variants of uncertain significance (VUS). Further research is needed around giving VUS results back to individuals, their ability to deal with uncertainty, the impact of this result, developing a robust platform for VUS monitoring and evolving an acceptable long-term management pathway for this.

3.3. Return of 'incidental' or 'secondary' findings of cancer gene mutations in population research studies

Some studies have offered return of incidental or secondary findings of post hoc genetic testing undertaken in patients recruited for other research purposes. Thompson et al undertook post-hoc genetic testing for *BRCA* mutations in 1997 women and Rowley et al reported testing in 5908 women over 40 years (mean age 59.2 years) undergoing mammographic screening for BC in the Australian Life-pool study.[77,78] Secondary findings of *BRCA* testing in 50,726 men and women have also been reported through the MyCode Community Health Initiative.[79,80] Preliminary outcomes from such

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studies show acceptability of returning clinically relevant genetic research results or secondary findings along-with engagement with screening/preventive services and are supportive of the concept of broadening access towards a population based approach. These studies give a good idea of mutation rates. In the 100,000 Genomes Project 'additional looked-for findings' are being offered as part of the whole genome analysis (and include 10 cancer-susceptibility genes).[81] Additionally in many studies the sub-groups opting for return of incidental/secondary looked-for findings are highly selective and not generalizable to an unselected unaffected general-population. For e.g. the 100,000 Genomes-Project is not a true population-cohort but comprises of individuals with cancer and families with rare paediatric diseases. However, this 'bolt-on' paradigm of returning additional secondary-findings is very different and not equivalent/identical to prospective uptake of testing CSGs in an unselected unaffected population. Data from these studies cannot be equated to outcomes of impact of true population-based testing. Such an approach does not address in an unbiased and prospective manner key questions of population testing around logistics; information giving, consent and true uptake; VUS management; and subsequent uptake of screening and prevention interventions. These outcomes could potentially be very different when apriori consent is sought for genetic testing for specific clinically actionable gene mutations, compared to vague/less-informed/un-informed consent related to imprecisely defined secondary outcomes in post-hoc research studies.

3.4. A potential strategy for chronic disease prevention

According to the US Centres for Disease Control & Prevention (CDC), 50% US adults have ≥1 and 25% US adults have ≥2 chronic health conditions and the latter accounts for >90% Medicare expenditure. CDC suggests that chronic diseases and injuries contributed to 2.7 million deaths in 2015.[82] Corresponding treatment costs and resulting lost productivity amounted to $1.3 trillion. In England chronic conditions account for 50% of GP appointments, 64% outpatient appointments, 70% inpatient bed days, and 70% of the total health and care spend.[83] The increasing prevalence of long-term/chronic conditions is the biggest challenge facing the UK National Health Service (NHS)[83] and many other health systems. Addressing this is critical to put health systems in a better position to remain viable for the future. The Milken Institute (a non-profit, nonpartisan economic think tank) have projected that by 2023 if we improved prevention, the US could avoid 40 million cases of chronic disease, cut treatment costs by $220 billion, and increase GDP by $900 billion.[84] According to the CDC commissioned National Vitals Statistics Reports the top five causes of deaths from chronic disease in 2015 were: 1) heart disease 2) cancer 3) lung disease 4) accidents 5) strokes.[82] Many of these can be prevented. WHO estimates that by 2030 the number of deaths due to heart disease, cancer, lung disease, accidents and strokes would rise by 24%, 37%, 32%, 14% and 29% in the Americas and by 23%, 45%, 41%, 23% and 28% worldwide respectively.[85] As validated disease specific models for risk prediction improve or develop and evolve, they can be used for population stratification to target the proportion of the population at highest risk of chronic disease. A prime example is cardiovascular disease. Testing for familial hypercholesterolemia could be added to any other genetic testing strategy. In addition going forward complex models incorporating epidemiological, lifestyle and single nucleotide polymorphism (SNP) data may reach broad mass based clinical applicability for population stratification and targeted primary prevention. A future population testing programme could target other diseases in addition to cancer. Implementing a new

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comprehensive population testing strategy can herald a paradigm change in approach which shifts/nudges the needle of healthcare towards prevention.

Addressing the increasing burden of chronic disease poses a major challenge for the future. Different organizations at times give conflicting recommendations which in turn can be exacerbated by the advocacy positions of special interest groups, leading to uncertainty amongst clinicians and inconsistent implementation. Clinicians due to increasing time pressures and employers/payers struggling with accelerating health care costs may question the value of some preventive interventions. Insurance coverage for individual preventive services, especially new technologies, is inconsistent.[86,87] Public messages conveyed are often inconsistent and increasingly coloured by commercial self-interest. Racial and ethnic minorities, socio-economically deprived and other underserved populations have a higher burden of chronic disease and need special attention to reach their full health potential.[88] To this end, it is vital to also address social determinants of health, including economic, social, and geographic factors that influence the health of populations and contribute to chronic diseases and injury.

3.5. Population Risk Stratification: beyond high penetrance genes

Newer risk prediction models incorporating validated SNPs (as a polygenic risk score) and epidemiological/clinical factors have improved the precision on individualised risk prediction. This allows division of the population into risk strata, such that the highest risk strata have a significant higher risk relative to the lower strata, enabling a) targeted risk stratified screening and/or b) targeted prevention for the higher risk strata, as long as the risks of individuals in these strata lie above a well-defined threshold of clinical utility (benefit and effectiveness). It may also identify a low-risk stratum who may benefit for less intense or no screening. This can be useful for making both individualised risk based decisions and population-based screening or prevention programmes. For example, models have been developed for breast, prostate and ovarian cancer. The Predicting the Risk of Cancer At Screening (PROCAS) study (UKCRN-ID 8080) showed that the addition of SNPs and mammographic breast density to the Tyrer-Cuzick model improves BC risk prediction and could be used for risk stratified screening in general-population women taking part in a national (NHS) Breast Screening Programme.[89] This was associated with lower- anxiety but slightly higher cancer worry than comparison women, with no consistent effect on intention to change behaviour, considerable variation in understanding of test results but high overall satisfaction.[90] The PROMISE Feasibility Study is evaluating the acceptability and feasibility of undertaking a study to stratify an unselected general population on the basis of their predicted lifetime OC-risk as well as offer risk management options of screening and prevention. The population is stratified into low (<5% OC-risk), intermediate (5-10% OC-risk) and high (>10% OC-risk) risk groups, using a model incorporating SNP based polygenic-risk score, *BRCA1*/*BRCA2*/*RAD51C*/*RAD51D*/*BIP1* mutations and epidemiological data. Personalised SNP based profiles are also being used for melanoma risk stratification. The SOMBRA (Skin health Online for Melanoma: Better Risk Assessment) RCT, investigates personalised SNP testing for melanoma risk versus un-tested controls,[91] in terms of short-term sun protection/self-examination, communication, beliefs, test comprehension/recall, satisfaction and cancer related distress following testing.[91] An Australian pilot RCT (ACTRN12615000356561), evaluated the

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feasibility and acceptability of communicating personalised SNP derived polygenic-risk scores for melanoma to the public, and its preliminary impact on health behaviour and psychosocial outcomes in 118 individuals.[92] Participants were randomised to intervention (personalised booklet & genetic counselling presenting melanoma polygenic risk) and control (non-personalised educational materials) arms.[92] Results showed no significant difference in behavioural effects, skin cancer related worry or psychological distress at 3 months.[92] A lot more research is needed to evaluate risk model based stratified screening and prevention, including implementation studies evaluating clinical effectiveness, impact, cost-effectiveness, health behaviour, psychology, ethical and social consequences.

4. Conclusions

Our healthcare structure is currently focused predominantly towards improving diagnosis & treatment of disease rather than illness prevention. The current clinical model for genetic testing is based on FH and serial referral through healthcare services. It requires people to develop cancer before identifying unaffected individuals in the family to target prevention. This process is inefficient, resource intense and misses a large proportion of individuals/mutation carriers at risk. Population testing can overcome these limitations. The ability to test populations on a large scale is now available, testing costs are falling and the acceptability/awareness of testing is rising. Population-based *BRCA* testing in the Jewish population has been extensively evaluated and found to be acceptable, feasible, clinically effective, safe, associated with high satisfaction rates and cost-effective. There are not many medical interventions that have the potential to save both lives and monies, but *BRCA*-testing in the Jewish population is one of them. Available data support change in guidelines to population based *BRCA* testing in the Jewish community.

Ongoing studies are evaluating population based genetic testing for CSGs in the general population. Initial analysis suggest this approach is potentially cost-effective for a panel of BC and OC gene mutations. The increasing appreciation and recognition of complexities of tumour heterogeneity, tumour evolution and resistant mutations associated with metastatic disease has moderated the initial anticipated impact of precision oncology driven drug therapy based approaches. Population-testing for established cancer-genes can provide an impetus to increase carrier detection-rates to maximise prevention and reduce cancer burden. A cancer prevention population-based genetic testing programme can serve as an important model, with programme outputs subsequently informing potential applicability and development of programmes for other chronic diseases.

While population testing holds great promise, several challenges need to be addressed along the way for this to materialise. To maximise the impact of population testing a future multi-gene and/or multi-disease panel testing approach/strategy needs to ensure: A) Clinical utility: Net clinical benefit on disease outcome taking into account benefits and harms of the intervention. B) Equal access: Ensuring equal access to disease prevention initiatives for all communities regardless of ethnicity, socio-economic background or gender, etc. C) Broadening research: For effective prevention and eradicating chronic disease it is critical to prioritise high quality research into disease prevention. There needs to be rebalancing of research funding from diagnosis/treatment towards prevention. For e.g., only 5% UK research funding goes into prevention.[93] The impact of panel germline population

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testing needs to be better understood and evaluated. D) Robust implementation pathways: these need to be context and health-system/population specific. E) Cost-effectiveness: Sustainable prevention strategies, need to be underpinned by evidence-based approaches that are economically viable and maximise the number of years lived in health. Policy makers and funders need to be educated about the significant cost savings that result from modest increases in prevention funding and potential savings & increased productivity that can result from employers/insurers/health funders promoting prevention. F) Consistent coherent messaging: Public messages need to be consistent, not be biased/swayed by commercial/vested interests, need to increase health professional and public awareness, and pay special attention to minority, socio-economically deprived and underserved populations or others with higher burden of disease.

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Literature search: FG, RM

Preparation of tables and figures: FG, RM

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Conflict of Interest Statement

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Ethics Approval Statement

This is a review of the published literature. Hence, no ethics approval was needed.

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